REMARKS

Claims 1 to 26 and 43 to 45, as amended, appear in this application for the Examiner's review and consideration. Claim 46 is canceled by this Amendment without prejudice to Applicants rights to file one or more divisional applications directed to the subject matter of that claim. The amendments are fully supported by the specification and claims as originally filed. In particular, the amendments to claims 1 and 15 are supported by the figures and the text of the specification describing the figures. The amendments to claim 5 are supported by paragraphs [0013]. [0036], and [0041] of the specification. The amendments to claim 20 are supported by paragraphs [0034] and [0043] of the specification. Therefore, there is no issue of new matter. In addition, the amendments to the independent claims add recitations that elaborate on the structure of the presently claimed invention, and, thus, do not affect the scope of the claims. The amendments only further clarify the claimed invention.

Claims 15 to 17 and 19 stand rejected under 35 U.S.C. § 102(b), as allegedly being anticipated by U.S. Patent No. 6,214,191 to Wiktorowicz et al. (Wiktorowicz), for the reasons set forth on pages 2 to 4 of the Office Action;

Claims 20 to 22, 24 and 46 stand rejected under 35 U.S.C. §103(a), as allegedly being unpatentable over Wiktorowicz for the reasons set forth on pages 4 to 7 of the Office Action;

Claim 1 to 7, 9, 10, 13, and 44 to 45 stand rejected under 35 U.S.C. § 103(a), as allegedly being unpatentable over Wiktorowicz in view of U.S. Patent Application Publication No. 2002/0162745 to Nordman et al. (Nordman) for the reasons set forth on pages 7 to 14 of the Office Action;

Claims 18 and 23 stand rejected under 35 U.S.C. § 103(a), as allegedly being unpatentable over Wiktorowicz in view of U.S. Patent No. 6,214,191 to Adcock, for the reasons set forth on pages 14 and 15 of the Office Action;

Claims 8 and 14 stand rejected under 35 U.S.C. § 103(a), as allegedly being unpatentable over Wiktorowicz in view of Nordman and further in view of Adcock, for the reasons set forth on pages 15 to 17 of the Office Action;

Claims 25 and 26 stand rejected under 35 U.S.C. § 103(a), as allegedly being unpatentable over Wiktorowicz in view of U.S. Patent No. 6,162,602 to Gautsch, for the reasons set forth on pages 17 and 18 of the Office Action; and

Claims 11 and 12 stand rejected under 35 U.S.C. § 103(a), as allegedly being unpatentable over Wiktorowicz in view of Nordman and further in view of Gautsch, for the reasons set forth on pages 18 and 19 of the Office Action.

Applicants submit that claim 46 has been cancelled, mooting the rejection of that claim.

In response to the rejections, Applicants submit that modifying a device disclosed in a reference in a manner requiring a redesign of the device that would change its principle of operation is improper in an obviousness rejection under 35 U.S.C. § 103(a). As stated in M.P.E.P. 2143.01(VI), citing *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (C.C.P.A 1959),

> If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious.

As cited by the M.P.E.P., the court in *Ratti* held that a suggested combination of references that would require a substantial reconstruction and redesign of the elements shown in the primary reference as well as a change in the basic principle under which the primary reference construction was designed to operate was not a proper ground for an obviousness rejection. M.P.E.P. 2143.01(VI), citing *In re Ratti*, 270 F.2d at 813, 123 USPQ at 352. Therefore, modifying the disclosure of Wiktorowicz in accordance with the disclosure of any of the other cited references or in a manner required to obtain the presently claimed invention that would change the principle of the operation of the devise disclosed by Wiktorowicz is impermissible for a rejection under 35 U.S.C. § 103(a), and does not provide a *prima facie* case of obviousness.

In addition, it is well settled law that a prior art reference must be considered as a whole, including those portions of the reference that would lead away from the claimed invention. M.P.E.P. § 2141.03 VI, citing *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984). The question under 35 U.S.C. § 103 is not whether differences between the prior art and the claimed invention would have been obvious, but whether the claimed invention as a whole would have been obvious. M.P.E.P. § 2141.02 I, citing *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); *Schenck v. Nortron Corp.*, 713 F.2d 782, 218 USPQ 698 (Fed. Cir. 1983)

It is also well settled law that a reconstruction of the claimed invention from the prior art based on the hindsight teaching of the Applicants' application is impermissible. M.P.E.P. § 2141.01(a) III, citing *Gore*. In particular, M.P.E.P. § 2142 states that, for a proper determination under 35 U.S.C. § 103(a),

> [T]he examiner must step backward in time and into the shoes worn by the hypothetical "person of ordinary skill in the art" when the invention was unknown and just before it was made. In view of all factual information, the examiner must then make a determination whether the claimed invention "as a whole" would have been obvious at that time to that person. Knowledge of applicant's disclosure must be put aside in reaching this determination, yet kept in mind in order to determine the "differences," conduct the search and evaluate the "subject matter as a whole" of the invention. The tendency to resort to "hindsight" based upon applicant's disclosure is often difficult to avoid due to the very nature of the examination process. However, impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art.

In the present case, the rejections of the claims over Wiktorowicz are the result of an impermissible hindsight reconstruction of the presently claimed invention, based on Applicants' disclosure. Those skilled in the art would have no reason to modify the device disclosed by Wiktorowicz to obtain the presently claimed invention without the teaching of the present specification. When considered as a whole, Wiktorowicz, whether taken alone or in combination with the other cited references, does not disclose or suggest the presently claimed invention, or provide any reason for one of ordinary skill in the art to obtain the presently claimed invention. Only the present specification provides the teaching required to obtain the presently claimed integrated microfluidic device.

In addition, the modifications required in the device disclosed by Wiktorowicz to obtain the presently claimed device would change the principle of operation of the device disclosed by Wiktorowicz, and, thus, the teachings of the Wiktorowicz and the other cited references are not sufficient to render the present claims *prima facie* obvious.

As recited in claim 1, the presently claimed invention is directed to an integrated microfluidic device. The claimed device comprises a sample loading chamber and a fluid reservoir connected by a microfluidic channel, where the microfluidic channel comprises an inlet and an outlet. The sample loading chamber is configured for loading a sample of charged molecules into the microfluidic device, is positioned at the inlet of the microfluidic channel, and comprises a first electrode and a second electrode configured to generate a first electric field in the sample loading chamber. The sample loading chamber defines an opening in an outer surface of the microfluidic device, where at least a portion of each of the first and second electrodes is in the opening, and, where, when generated, the first electric field is configured to transfer charged molecules in the sample loading chamber to the inlet of

the microfluidic channel. The fluid reservoir is configured for unloading a sample of charged molecules from the microfluidic device, is positioned at the outlet of the microfluidic channel, and comprises a third electrode configured to generate a second electric field with at least the second electrode.

Claim 5 differs from claim 1 in that claim 5 recites a section of matrix material comprising charged molecules in the sample loading chamber, where the section of matrix material is configured for loading the charged molecules into the sample loading chamber of the microfluidic device, and, when generated, the first electric field is configured to electro-elute the charged molecules from the section of matrix material and to transfer the charged molecules to the inlet of the microfluidic channel. Claim 5 also differs from claim 1 in that claim 5 does not recite that the sample loading chamber defines an opening in an outer surface of the microfluidic device, where at least a portion of each of the first and second electrodes is in the opening.

Claim 15 differs from claim 1 in that claim 15 recites a sample unloading chamber rather than a sample loading chamber, and that the fluid reservoir is positioned at the inlet of the microfluidic channel and comprises a third electrode. The sample unloading chamber is configured for unloading a sample of charged molecules from the microfluidic device, and is positioned at the outlet of the microfluidic channel. The sample unloading chamber comprises the first and second electrodes, which are configured to generate a first electric field in the sample unloading chamber. It is the sample unloading chamber that defines an opening in an outer surface of the microfluidic device, where at least a portion of each of the first and second electrodes is in the opening, and, where, when generated, the first electric field is configured to transfer charged molecules from the outlet of the microfluidic channel into the sample unloading chamber.

Claim 20 differs from claim 15 in that claim 20 recites a section of matrix material in the sample unloading chamber, where the section of matrix material is configured for unloading the charged molecules from the sample unloading chamber of the microfluidic device, and, when generated, the first electric field is configured to transfer charged molecules from the outlet of the microfluidic channel into the section of matrix material, thereby providing for unloading the charged molecules from the microfluidic device in the section of matrix material. Claim 20 also differs from claim 15 in that claim 20 does not recite that the sample unloading chamber defines an opening in an outer surface of the microfluidic device, where at least a portion of each of the first and second electrodes is in the opening.

In contrast to the presently claimed integrated microfluidic device, Wiktorowicz discloses methods and apparatus for conducting multidimensional electrophoresis of samples within a single apparatus. With the disclosed device, sample components that have been resolved in a first electrophoretic dimension can be directly electrophoresed in a second dimension that is substantially perpendicular to the first. Wiktorowicz discloses that there is no need to move or manipulate the sample between the first and second electrophoretic steps with the disclosed device. Wiktorowicz, column 2, line 64, to column 3, line 4. The device disclosed by Wiktorowicz that is cited in the Office Action is illustrated in Figures 3 and 4 of Wiktorowicz, which are reproduced below.

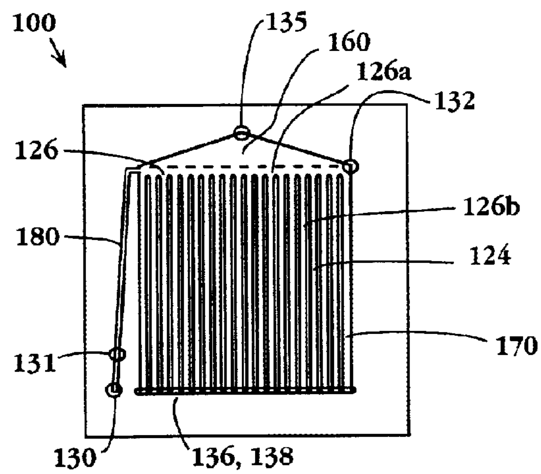

Fig. 3

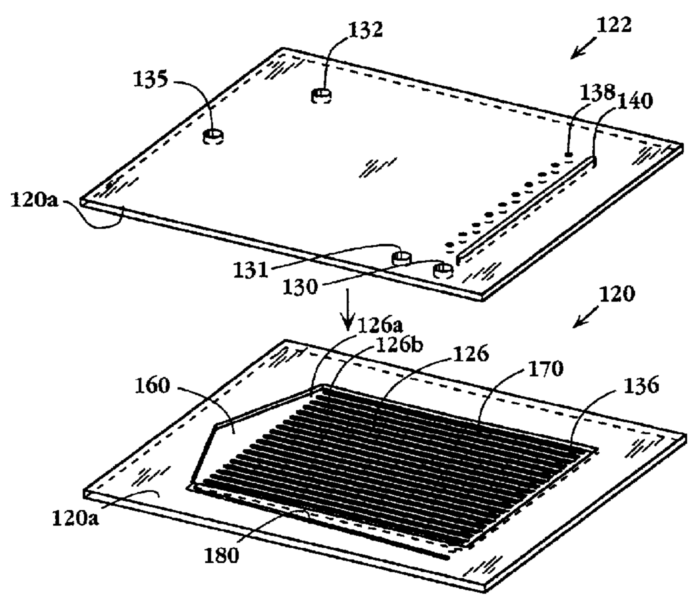

Fig. 4

As illustrated, the disclosed device has a bottom plate 120, containing a recessed region 126 that includes a first sample separation surface 126a, for electrophoresis along the lateral dimension of this region, and a second sample separation surface 126b for isoelectric focusing, and surface 126b comprises a plurality of parallel separation channels 170 that are aligned in a direction perpendicular to the bottom edge of the plate. Region 126 also has a fan-shaped liquid loading region 160 at the upper end of the plate, for introducing and removing separation media to and from the separation cavity before and after electrophoresis. Wiktorowicz, column 6, lines 54 to 64, and column 7, lines 1 to 4. When considered as a whole, one of ordinary skill in the art would understand that the region 160 is not a sample loading chamber or a sample unloading chamber, and would not function as such a sample loading or unloading chamber in the disclosed device.

Wiktorowicz discloses that sample resolution increases as the number of channels 170 is increased, subject to the limit of resolution achieved by electrophoresis in the first, lateral, dimension, where the channels are preferably dimensioned so that the channel resolution is at least twice the sample resolution in the lateral dimension of the separation medium, so that each sample band partitions into from one to three channels. Wiktorowicz, column 7, lines 18 to 24.

As illustrated in Figures 3 and 4, the plate 120 has an elongate sample transport channel 180 that extends from the lower left hand portion of the plate 120 to the upper left hand corner of surface 126a for size-based electrophoretic separation of the sample during transit to the separation cavity 124. Wiktorowicz, column 7, lines 25 to 29. In its lower left corner, plate 122 defines a sample loading port 130 through which samples are introduced into the separation cavity, and provides access to the separation cavity for a first electrode 130a for establishing a voltage potential at the loading port. Wiktorowicz, column 7, lines 40 to 44.

The plate 122 also defines an electrode port 132 in the upper right corner of plate for a second electrode 132a in electrical contact with the separation cavity. Electrodes 130a and 132a are not illustrated in the Figures. Wiktorowicz discloses that the first and second electrodes 130a and 132a are used for performing electrophoresis of the sample along a first dimension, stretching from port 130 to port 132, to generate a series of separated sample components along the upper edge of 126a after the first electrophoresis step is complete. Wiktorowicz, column 7, lines 40 to 52.

Wiktorowicz discloses the port 135 in plate 122 for transporting separation media and wash fluids into and out of the separation cavity, and an elongate slot 140 that extends laterally along the bottom of the plate 122. Wiktorowicz, column 7, line 44 to 57.

Wiktorowicz discloses that plate 122 may also define a waste port 131 in fluid communication with the elongate sample transport channel 180 and port 130 to allow a precise amount of sample to be injected into channel 180. Wiktorowicz, column 7, lines 58 to 62. The plates 120 and 122 also define channel egress ports 136 and 138 that are located slightly above slot 140 for collecting the sample components from one or more channels after both separation steps are complete. Wiktorowicz, column 7, lines 63 to 67.

Wiktorowicz discloses that samples and separation media are introduced into the disclosed device as follows: A low-ionic strength solution is loaded into the separation cavity via ports 130 and 135, with egress through the egress ports 138, until residual air bubbles have been removed from the cavity. The egress ports are then closed, and valves at ports 130, 132, and 135 are opened to admit a second electrophoresis solution via port 135 into regions 160 and 126a and elongate channel 180. The second solution is preferably a low pH, flowable entangled polymer solution, as above, for effecting size-based separation in the first dimension. Wiktorowicz, column 14, lines 40 to 50.

With the plate equilibrated with the appropriate solutions, sample injection is accomplished by hydrodynamic or electrophoretic means, where hydrodynamic injection is performed by closing all ports and slot(s) except ports 130 and 131, and pumping a selected volume of sample through the portion of channel 180 located between ports 130 and 131. The sample is then moved into the portion of channel 180 beyond port 131 by closing port 131, opening port 132, and pumping the appropriate volume of buffer solution through port 130. Electrophoretic sample injection is accomplished by filling the portion of channel 180 beyond port 131 with a selected amount of sample via ports 130 and 131, as above, closing those ports, and then applying an electric field between ports 130 and 132, such that a small amount of positively charged sample migrates into the separation channel upstream of port 131. Wiktorowicz, column 14, line 63, to column 15, line 17.

Wiktorowicz then discloses that, after the sample is loaded, electrophoresis is performed in a first dimension across region 126a by applying an electric field between ports 130 and 132, such that injected sample components migrate through channel 180 and into region 126a towards the electrode 132a at port 132. When the fastest migrating component reaches port 132, the field is turned off, and a new field is applied across region 126 in a direction substantially perpendicular to the first dimension, where the field is generated by:

Balancing the electric potentials at ports 130 and 132 to establish a substantially uniform field vertically across regions 126a and 126b towards slot 140;

Using an elongate wire electrode which (i) is electrically isolated from point electrodes located at ports 130 and 132, (ii) enters region 126a via port 132, and (iii) spans the upper edge of region 126a; or

Using electrodes located at port 135 and slot 140.

Wiktorowicz discloses that the conventional approach to two-dimensional electrophoresis is to perform the first dimension in a rigid, usually cross-linked matrix. Wiktorowicz, column 2, lines 24 to 26. However, with regard to the disclosed device, at column 17, lines 42 to 45, Wiktorowicz discloses

> The apparatus is simple to use and can generate analytical results more rapidly than previous two-dimensional methods. The method permits characterization of samples containing hundreds or thousands of components under a variety of different separation conditions. The method ***does not require a crosslinked matrix***, and therefore is easily refilled with the same or different media for separating additional samples. (emphasis added)

Therefore, Wiktorowicz discloses a device configured for two-dimensional electrophoresis that does not require matrix material as a separation medium or for any other purpose. Separation media, i.e., electrophoresis solutions, are introduced into the disclosed device through ports 130 and 135. Separation media introduced into the disclosed device through port 135 then enter a fan-shaped liquid loading region 160 at the upper end of the plate. Samples to be separated by electrophoresis are introduced through a sample loading port 130 defined by plate 122. Electrodes 130a and 132a are used to generate an electric field between port 130 and 132, resulting in electrophoresis that separates the samples by size as they travel trough elongate channel 180 toward port 132. Electrodes, such as those at ports 135 and 140 are then used to separate the sample in a second dimension through separation channels 170. The separated sample is removed from the disclosed device through egress ports 136 and 138, which do not contain electrodes.

When the disclosure of Wiktorowicz is considered as a whole, one of ordinary skill in the art will understand that the principle of operation of the disclosed device requires samples to be introduced through the sample loading port 130, and, after separation in two dimensions, removed from the disclosed device through egress ports 136 and 138. The principle of operation of the disclosed device does not allow samples to be loaded into or unloaded from region 160.

One of ordinary skill in the art following the disclosure of Wiktorowicz without the benefit of the disclosure of the present application would understand that the only sample input port disclosed by Wiktorowicz is port 130, and the only egress ports are ports 136 and 138. One of ordinary skill in the art would not consider region 160 to be a sample loading chamber or a sample unloading chamber.

Although Wiktorowicz discloses that the fan-shaped liquid loading region 160 is for introducing and removing separation media to and from the separation cavity before and after electrophoresis, Wiktorowicz clearly discloses that electrophoresis solutions are introduced through 130 and 135, and are allowed to flow through the egress ports until all air bubbles are removed from the cavity. Samples are introduced through port 130 or, perhaps, port 131, such that a volume of the sample is introduced into the portion of channel 180 located between ports 130 and 131. A first electrophoretic separation of the sample in a first dimension is performed by producing an electric field between electrodes 130a and 132a. A second electrophoretic separation of the sample in a second dimension is performed by producing an electric field, as described above, such as between electrodes in port 135 and slot 140.

Thus, one of ordinary skill in the art will understand that introducing or removing samples from region 160 would change the principle of operation of the device disclosed by Wiktorowicz. That is improper for a rejection under 35 U.S.C. § 103(a). *See* M.P.E.P. 2143.01(VI). The clear purpose of the device disclosed by Wiktorowicz, when that reference is considered as a whole, is to obtain two separate electrophoresis separation in two different directions in the same device.

Assuming for the sake of argument that it is possible to introduce or remove samples from region 160, introduction or removal of the samples in that region would only allow a single separation, either through channel 180 or through one or more of channels 170. That is an impermissible change in the principle of operation of the device. Wiktorowicz does not disclose that region 160 is a sample loading chamber or sample unloading chamber, and provides no reason for one of ordinary skill in the art to consider the region 160 as a sample loading chamber or sample unloading chamber. One of ordinary skill in the art, considering the disclosure of Wiktorowicz as a whole, would understand that the principle of operation of disclosed device requires the introduction of sample through input port 130 and removal of separated samples through egress ports 136 and 138, such that two separations on the samples in two dimensions are obtained.

In addition, region 160 could only be considered to be a sample loading chamber or sample unloading chamber based on an impermissible hindsight reconstruction of the presently claimed integrated microfluidic device based on the disclosure and claims of the present application. Region 160 possibly contains two electrodes, as Wiktorowicz discloses that ports 132 and 135 contain electrodes, and an electrode that spans the upper edge of region 126a may optionally be used. Present claims 1 and 5 recite first and second electrodes in a sample loading chamber, and present claims 15 and 20 recite first and second electrodes in a sample unloading chamber. Therefore, the Office Action declares that region 160 must be a sample loading chamber or sample unloading chamber.

Such statements in the Office Action are clearly based on the disclosure of the present specification and the recitations of the present claims, and, thus, are an impermissible hindsight reconstruction of the presently claimed integrated microfluidic device based on the present disclosure. Such statements are clearly not based on the disclosure of Wiktorowicz. When considered as a whole, Wiktorowicz does not disclose or suggest an input port, other than port 130, and does not disclose or suggest an output port other than the egress ports 136 and 138.

With regard to the matrix material recited in the present claims, Wiktorowicz specifically discloses that a matrix material is not required in the disclosed device. As a result, the device is easily refilled with the same or different media for separating additional samples. Using matrix material as a separation material would impermissibly change the principle of operation of the disclosed device. Therefore, Wiktorowicz provides no reason for one of ordinary skill in the art to use a matrix material in the disclosed device.

However, present claims 5 and 20 recite that the sample loading chamber (claim 5) and the sample unloading chamber (claim 20) comprise a portion of matrix material. As recited in claim 5, the section of matrix material is configured for loading the charged molecules into the sample loading chamber of the microfluidic device. As recited in claim 20, the section of matrix material is configured for unloading the charged molecules into the sample loading chamber of the microfluidic device.

Therefore, the Office Action declares that it would have been obvious to use a matrix material in the device disclosed by Wiktorowicz. Such statements in the Office Action are clearly based on the disclosure of the present specification and the recitations of the present claims, and, thus, are an impermissible hindsight reconstruction of the presently claimed integrated microfluidic device based on the present disclosure.

Such statements are clearly not based on the disclosure of Wiktorowicz. When considered as a whole, Wiktorowicz discloses that a matrix material is not used in the device. Moreover, Wiktorowicz discloses that it is conventional to use a matrix material as an electrophoresis medium. Wiktorowicz does not disclose or suggest a section of matrix material configured for loading (unloading) the charged molecules into (from) a sample (un)loading chamber of a microfluidic device, as presently claimed.

Wiktorowicz, whether taken alone or in combination with the other cited references, does not disclose or suggest the presently claimed integrated microfluidic device. Any modification of the device disclosed by Wiktorowicz to obtain the presently claimed integrated microfluidic device is an improper hindsight reconstruction of the present claims based on the disclosure of the present specification, and would improperly change the principle of operation of the disclosed device.

With regard to the rejection of claims 15 to 17 and 19 under 35 U.S.C. § 102(b), as discussed above, Wiktorowicz fails to disclose a sample unloading chamber, comprising first and second electrodes, configured to generate a first electric field in the sample unloading chamber, where the first electric field is configured to transfer charged molecules from the outlet of the microfluidic channel into the sample unloading chamber, as presently claimed. The only unloading ports disclosed by Wiktorowicz are the egress ports 136 and 138. The region 160 can only be considered to be a sample unloading chamber based on an improper hindsight reconstruction of the present claims based on the disclosure of the present specification and the present claims. The region 160 is not a sample unloading chamber, as presently claimed, and Wiktorowicz does not disclose that the region 160 is a sample unloading chamber.

However, to expedite the early allowance of the claims, Applicants have amended claim 15 to recite that the sample unloading chamber defines an opening in an outer surface of the microfluidic device, and at least a portion of each of the first and second electrodes is in the opening. In contrast to the presently claimed integrated microfluidic device, Wiktorowicz only discloses ports containing a single electrode, where the port defines an opening in an outer surface of the disclosed device. Wiktorowicz does not disclose the presently claimed integrated microfluidic device.

As Wiktorowicz does not disclose the presently claimed integrated microfluidic device, the claims are not anticipated by that reference. Accordingly, it is respectfully requested that the Examiner withdraw the rejection of claims 15 to 17 and 19 under 35 U.S.C. § 102(b) over Wiktorowicz.

With regard to the rejection of claims 20 to 22, 24 and 46 under 35 U.S.C. §103(a) over Wiktorowicz, as discussed above, the region 160 is not a sample unloading chamber, as presently claimed, and Wiktorowicz does not disclose or suggest that the region 160 is a sample unloading chamber. The region 160 can only be considered to be a sample unloading chamber based on an improper hindsight reconstruction of the present claims based on the disclosure of the present specification and the present claims. In addition, using the region 160 as a sample unloading chamber, if that was possible, would impermissibly change the principle of operation of the disclosed device. Therefore, any rejection of the claims based on region 160 being a sample unloading chamber is improper.

Moreover, as discussed above, with regard to the matrix material recited in the present claims, Wiktorowicz specifically discloses that a matrix material is not required in the disclosed device. As a result, the device is easily refilled with the same or different media for separating additional samples. Using matrix material as a separation material would impermissibly change the principle of operation of the disclosed device. Therefore, Wiktorowicz provides no reason for one of ordinary skill in the art to use a matrix material in the disclosed device.

In addition, Wiktorowicz discloses that, in the prior art, matrix materials were used as separation media. That is not the presently claimed invention. In the presently claimed integrated microfluidic device, the section of matrix material of the presently claimed integrated microfluidic device is configured for unloading the charged molecules from the sample unloading chamber of the microfluidic device, thereby providing for unloading the charged molecules from the microfluidic device in the section of matrix material. Wiktorowicz does not disclose or suggest a section of matrix material configured for unloading charged molecules from a sample unloading chamber of a microfluidic device, thereby providing for unloading the charged molecules from the microfluidic device in the section of matrix material, as presently claimed, and fails to provide any reason for one of ordinary skill in the art to do so.

Therefore, as Wiktorowicz does not disclose or suggest a section of matrix material configured for unloading charged molecules from a sample unloading chamber of a microfluidic device, thereby providing for unloading the charged molecules from the microfluidic device in the section of matrix material, as presently claimed, and fails to provide any reason for one of ordinary skill in the art to do so, the present claims are not obvious over that reference. Accordingly, it is respectfully requested that the Examiner

withdraw the rejection of claims 20 to 22, 24 and 46 under 35 U.S.C. § 103(a) over Wiktorowicz.

With regard to the rejection of claims 1 to 7, 9, 10, 13, and 44 to 45 under 35 U.S.C. § 103(a) over Wiktorowicz and Nordman, as discussed above, Wiktorowicz fails to disclose a sample loading chamber, comprising first and second electrodes, configured to generate a first electric field in the sample loading chamber, where the first electric field is configured to transfer charged molecules in the sample loading chamber the inlet of the microfluidic channel, as presently claimed. The only loading port disclosed by Wiktorowicz is port 130. The region 160 can only be considered to be a sample loading chamber based on an improper hindsight reconstruction of the present claims based on the disclosure of the present specification and the present claims. The region 160 is not a sample loading chamber, as presently claimed, and Wiktorowicz does not disclose or suggest that the region 160 is a sample loading chamber.

In addition, the use of the region 160 as a sample loading chamber, if possible, would impermissibly change the principle of operation of the device disclosed by Wiktorowicz. Using the region 160 as a sample loading chamber would not allow separation in two dimensions, as disclosed by Wiktorowicz. Any modification of the disclosure of Wiktorowicz to obtain the presently claimed integrated microfluidic device is improper. Wiktorowicz provides no reason for one of ordinary skill in the art to obtain the presently claimed integrated microfluidic device.

However, to expedite the early allowance of the claims, Applicants have amended claim 1 to recite that the sample loading chamber defines an opening in an outer surface of the microfluidic device, and at least a portion of each of the first and second electrodes is in the opening. In contrast to the presently claimed integrated microfluidic device, Wiktorowicz only discloses ports containing a single electrode, where the port defines an opening in an outer surface of the disclosed device. Wiktorowicz, whether taken alone or in combination with the other cited references, does not disclose or suggest the presently claimed integrated microfluidic device, and provides no reason for one of ordinary skill in the art to do obtain the presently claimed integrated microfluidic device.

In addition, as discussed above, claim 5 recites a section of matrix material in the sample loading chamber configured for loading the charged molecules into the sample loading chamber of the microfluidic device. Wiktorowicz does not disclose or suggest a section of matrix material in a sample loading chamber configured for loading the charged molecules into the sample loading chamber of the microfluidic device, and also discloses that

the disclosed device does not require a cross-linked matrix. The elimination of the requirement for a cross-linked matrix material for separations allows the device to be easily refilled with media for separating additional samples. One of ordinary skill in the art, following the disclosure of Wiktorowicz, whether taken alone or in combination with the other cited references, would have no reason to place a section of matrix material in a sample loading chamber configured for loading the charged molecules into the sample loading chamber of the microfluidic device, as presently claimed.

Nordman does nothing to overcome the deficiencies of Wiktorowicz. As cited by the Office Action, Nordman may disclose a channel electrophoresis device in which the interface between the microchannels and the fluid reservoir is modified to control distortion of separated sample to enhance detectability. As discussed above, any rejection of the present claims over Wiktorowicz is improper, as being an improper hindsight reconstruction of the presently claimed integrated microfluidic device based on the disclosure of the present application, and for requiring an impermissible change in the principle of operation of the device disclosed by Wiktorowicz. When the disclosure of Wiktorowicz is considered as a whole without the teaching of the present application, one of ordinary skill in the art combining the disclosure of Nordman with that of Wiktorowicz would not obtain the presently claimed integrated microfluidic device. The resulting device would not have the presently claimed sample loading chamber defining an opening in an outer surface of the microfluidic device, and comprising first and second electrodes in the opening, as recited in claim 1, and would not contain the section of matrix material in the sample loading chamber, as recited in claim 5.

Therefore, Wiktorowicz and Nordman, whether taken alone or in combination, do not disclose or suggest the presently claimed integrated microfluidic device, and fail to provide any reason to obtain the presently claimed integrated microfluidic device. Accordingly, it is respectfully requested that the Examiner withdraw the rejection of claims 1 to 7, 9, 10, 13, and 44 to 45 under 35 U.S.C. § 103(a) over Wiktorowicz and Nordman.

With regard to the rejection of claims 18 and 23, claim 18 depends from claim 15 through claim 17, and, thus, includes the claim element that the sample unloading chamber defines an opening in an outer surface of the microfluidic device, where at least a portion of each of the first and second electrodes is in the opening. Claim 23 depends from claim 20 through claims 21 and 22, and, thus, includes the claim limitation that the sample unloading chamber includes a section of matrix material, where the section of matrix material is configured for unloading the charged molecules from the sample unloading chamber of the

microfluidic device, thereby providing for unloading the charged molecules from the microfluidic device in the section of matrix material. Applicants submit that, for the reasons set forth above, claims 15, 17, and 20 to 22 are not obvious over Wiktorowicz.

Wiktorowicz does not disclose or suggest a sample unloading chamber in a microfluidic device, defining an opening in an outer surface of the microfluidic device, where at least a portion of each of the first and second electrodes is in the opening, as recited in claim 15. Wiktorowicz also fails to disclose or suggest a sample unloading chamber in a microfluidic device, comprising a section of matrix material, configured for unloading the charged molecules from the sample unloading chamber of the microfluidic device, thereby providing for unloading the charged molecules from the microfluidic device in the section of matrix material, as recited in claim 20.

Adcock does nothing to overcome the deficiencies of Wiktorowicz. As cited in the Office Action, Adcock may disclose a method of field inversion electric pulses to force DNA or protein out of a gel and into an appropriate receiver, where the inverted pulsed electric field allows for the electro-elution of higher molecular weights, i.e., 2×10^4 base pairs. However, Adcock fails to disclose or suggest the presently claimed sample unloading chamber in a microfluidic device, defining an opening in an outer surface of the microfluidic device, where at least a portion of each of the first and second electrodes is in the opening, as recited in claim 15, or the sample unloading chamber in a microfluidic device, comprising a section of matrix material, configured for unloading the charged molecules from the sample unloading chamber of the microfluidic device, thereby providing for unloading the charged molecules from the microfluidic device in the section of matrix material, as recited in claim 20. Even if the disclosures of Adcock and Wiktorowicz were combined, the resulting combination would not provide the presently claimed integrated microfluidic device, and would provide no reason for one of ordinary skill in the art to obtain the presently claimed integrated microfluidic device.

Therefore, as Wiktorowicz and Adcock, whether taken alone or in combination, do not disclose or suggest the presently claimed integrated microfluidic device, and fail to provide one of ordinary skill in the art any reason for one of ordinary skill in the art to obtain the claimed device, the present claims are not obvious over those references. Accordingly, it is respectfully requested that the Examiner withdraw the rejection of claims 18 and 23 under 35 U.S.C. § 103(a) over Wiktorowicz in view of Adcock.

With regard to the rejection of claims 8 and 14 under 35 U.S.C. § 103(a) over Wiktorowicz, Nordman, and Adcock, each of those claims depend from claim 5, which is not

obvious over Wiktorowicz and Nordman for the reasons set forth above. Claim 5 discloses a sample loading chamber, comprising a section of matrix material that is configured for loading charged molecules into the sample loading chamber of the microfluidic device. As discussed above, Wiktorowicz and Nordman, whether taken alone or in combination, do not disclose the sample loading chamber of the presently claimed integrated microfluidic device.

Adcock does nothing to overcome the deficiencies of Wiktorowicz and Nordman. As cited in the Office Action, Adcock may disclose a method of field inversion electric pulses to force DNA or protein out of a gel and into an appropriate receiver, where the inverted pulsed electric field allows for the electro-elution of higher molecular weights, i.e., $2 \text{ X } 10^4$ base pairs. However, Adcock does not disclose or suggest a sample loading chamber in a microfluidic device, comprising a section of matrix material that is configured for loading charged molecules into the sample loading chamber of the microfluidic device, as recited in claim 5. Even if the disclosure of Adcock was combined with those of Wiktorowicz and Nordman, the resulting combination would not provide the presently claimed integrated microfluidic device, and would not provide any reason for one of ordinary skill in the art to obtain the presently claimed invention.

Therefore, as Wiktorowicz, Nordman, and Adcock, whether taken alone or in combination, do not disclose or suggest the presently claimed integrated microfluidic device, and provide no reason for one of ordinary skill in the art to obtain the presently claimed invention, the present claims are not obvious over those references. Accordingly, it is respectfully requested that the Examiner withdraw the rejection of claims 8 and 14 under 35 U.S.C. § 103(a) over Wiktorowicz, Nordman, and Adcock.

With regard to the rejection of claims 25 and 26 under 35 U.S.C. § 103(a), over Wiktorowicz in view of Gautsch, claims 25 and 26 depend from claim 20, and, thus, include the limitation that sample unloading chamber includes a section of matrix material, where the section of matrix material is configured for unloading the charged molecules from the sample unloading chamber of the microfluidic device, thereby providing for unloading the charged molecules from the microfluidic device in the section of matrix material. As discussed above, Wiktorowicz fails to disclose or suggest a sample unloading chamber in a microfluidic device, comprising a section of matrix material, configured for unloading the charged molecules from the sample unloading chamber of the microfluidic device, thereby providing for unloading the charged molecules from the microfluidic device in the section of matrix material.

Gautsch does nothing to overcome the deficiencies of Wiktorowicz. As cited in the Office Action, Gautsch may disclose a method for nucleic acid base sequencing in which fragments are separated by means of capillary electrophoresis employing agarose or polyacrylamide gel. Applicants respectfully submit that the combination of the disclosure of Gautsch with that of Wiktorowicz is improper, and, even if the disclosures were combined, the resulting combination would not provide the presently claimed integrated microfluidic device.

As discussed above, when the disclosure of Wiktorowicz is considered as a whole, one of ordinary skill in the art following the disclosure of Wiktorowicz would not use a matrix material as a separation material. Such a use of a matrix material would impermissibly change the principle of operation of the disclosed device. In addition, the present claims do not recite the use of a matrix material as a separation material. Instead, the present claims recite a section of matrix in the sample unloading chamber that is configured for unloading the charged molecules from the sample unloading chamber of the microfluidic device. The cited art does not disclose or suggest such a section of matrix material, and provides no reason for one of ordinary skill in the art to obtain the presently claimed integrated microfluidic device.

Therefore, as Wiktorowicz and Gautsch, whether taken alone or in combination, do not disclose or suggest a section of matrix in a sample unloading chamber that is configured for unloading charged molecules from the sample unloading chamber of a microfluidic device, and provide no reason for one of ordinary skill in the art to obtain the presently claimed integrated microfluidic device, the present claims are not obvious over those references. Accordingly, it is respectfully requested that the Examiner withdraw the rejection of claims 25 and 36 under 35 U.S.C. § 103(a) over Wiktorowicz and Gautsch.

With regard to the rejection of claims 11 and 12 under 35 U.S.C. § 103(a) over Wiktorowicz in view of Nordman and further in view of Gautsch, the base claim for those claims is claim 5. Therefore, claims 11 and 12 include the claim element a section of matrix material in the sample loading chamber, where the section of matrix material is configured for loading the charged molecules into the sample loading chamber of the microfluidic device. As discussed above, Wiktorowicz and Nordman, whether taken alone or in combination, do not disclose or suggest an integrated microfluidic device having a section of matrix material in a sample loading chamber, where the section of matrix material is configured for loading charged molecules into a sample loading chamber of the microfluidic

device, as presently claimed, and fail to provide one of ordinary skill in the art to obtain the presently claimed device.

Gautsch does nothing to overcome the deficiencies of Wiktorowicz and Nordman. As cited in the Office Action, Gautsch may disclose a method for nucleic acid base sequencing in which fragments are separated by means of capillary electrophoresis employing agarose or polyacrylamide gel. As discussed above, Applicants respectfully submit that the combination of the disclosure of Gautsch with that of Wiktorowicz is improper, and, even if the disclosures were combined, the resulting combination would not provide the presently claimed integrated microfluidic device.

Therefore, as Wiktorowicz, Nordman, and Gautsch, whether taken alone or in combination, do not disclose or suggest the presently claimed integrated microfluidic device, and fail to provide any reason for one of ordinary skill in the art to obtain the presently claimed device, the present claims are not obvious over those references. Accordingly, it is respectfully requested that the Examiner withdraw the rejection of claims 11 and 12 under 35 U.S.C. § 103(a) over Wiktorowicz, Nordman, and Gautsch.

Applicants thus submit that the entire application is now in condition for allowance, an early notice of which would be appreciated. Should the Examiner not agree with Applicants' position, a personal or telephonic interview is respectfully requested to discuss any remaining issues prior to the issuance of a further Office Action, and to expedite the allowance of the application.

No fee is believed to be due for the filing of this Amendment. Should any fees be due, however, please charge such fees to Deposit Account No. 11-0600.

Respectfully submitted,

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Dated: July 8, 2009 By: /Alan P. Force/

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